

CORRESPONDENCE



Bivalirudin in Acute Coronary Syndromes

TO THE EDITOR: Valgimigli et al. (Sept. 10 issue)¹ report that prolongation of the bivalirudin infusion after the completion of coronary intervention did not significantly reduce the risk of early stent thrombosis with bivalirudin as compared with the periprocedural use of unfractionated heparin. The rapid and opposing endothelial effects of bivalirudin and heparin have been described previously.² Bivalirudin enhances the vascular sequestration of neutrophil-derived myeloperoxidase, which has the effect of accelerating the consumption of nitric oxide and depressing its bioavailability.² In contrast, heparin liberates vessel-bound myeloperoxidase and improves endothelial function.² The bivalirudin–myeloperoxidase–nitric oxide interaction may predispose

patients to early stent thrombosis during acute myocardial infarction. First, neutrophil activation is an early event in acute myocardial infarction.³ Second, interactions between activated platelets and neutrophils stimulate the formation of so-called neutrophil extracellular traps (chromatin filaments released from neutrophils) bearing active tissue factor in the infarct-related artery,⁴ which further induces thrombin generation and platelet activation. Third, blockade of the platelet P2Y₁₂-receptor boosts the capacity of nitric oxide to inhibit thrombin-stimulated platelet activation and aggregation by a factor of 1000 to 100,000.⁵ Thus, the bivalirudin-mediated vascular immobilization of neutrophil-derived myeloperoxidase might contribute to early stent thrombosis during acute myocardial infarction as a result of the inactivation of endogenous nitric oxide that occurs before there is fully effective platelet inhibition, just after loading doses of oral P2Y₁₂ antagonists have been administered.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In a post hoc analysis, the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) investigators found that the risk of acute stent thrombosis can be eliminated by means of the continued use of a full dose of bivalirudin (1.75 mg per kilogram of body weight per hour) after percutaneous coronary intervention (PCI), but not a reduced dose (0.25 mg per kilogram of body weight per hour).¹ The Bivalirudin in Acute Myocardial Infarction vs. Glycoprotein IIb/IIIa and Heparin: A Randomized Controlled Trial (BRIGHT) investigators therefore mandated in their protocol that only a full dose of bivalirudin should be continued after PCI, which eliminated the increased risk of acute stent thrombosis as compared with heparin in that trial.² Unfortunately, the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) investigators let individual practitioners select the doses of bivalirudin, which led the majority of practitioners to use reduced doses. MATRIX only proved that a reduced dose of bivalirudin does not prevent acute stent thrombosis; it did not disprove the beneficial effect of a full dose of bivalirudin, as was observed in the BRIGHT trial. Even the MATRIX study suggested a dose-response phenomenon: as shown by Valgimigli et al. in Table S5 in the Supplementary Appendix of their article (available at NEJM.org), the incidence of definite stent thrombosis in the group receiving the full dose of bivalirudin was lower than it was in the reduced-dose group (0.2% vs. 2.1%). If the MATRIX investigators had used a full dose of bivalirudin for all their patients, their results might have been different.

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2. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015;313:1336-46.

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THE AUTHOR AND A COLLEAGUE REPLY: Surdacki et al. speculate that the null effect of the post-PCI infusion of bivalirudin on ischemic events observed in the MATRIX trial is due to an interaction between bivalirudin and myeloperoxidase. In particular, the authors mention the role of bivalirudin in the sequestration of neutrophil-derived myeloperoxidase,¹ which reduces the availability of nitric oxide. It remains unclear whether this observation pertains to patients with acute coronary syndromes, since these data were generated primarily in vitro and were only partially corroborated in 30 patients undergoing elective PCI. This biochemical finding was observed only in patients receiving the full dose of bivalirudin (0.75 mg per kilogram followed by an infusion of 1.75 mg per kilogram per hour), and it is explained by the stoichiometric sequestration of myeloperoxidase by bivalirudin, which is presumably a dose-related effect.¹ Hence, a lower-dose regimen of bivalirudin, such as the 0.25 mg per kilogram per hour used in the MATRIX trial, should minimize the risk of the stoichiometric sequestration of myeloperoxidase.

However, like others,^{2,3} we have observed an excess of ischemic events in patients receiving the low post-PCI dose of bivalirudin or no post-PCI bivalirudin, but not during PCI or in those receiving the full-dose PCI-bivalirudin regimen after intervention. Hence, the myeloperoxidase interaction is unlikely to explain our results. The absence of bivalirudin (or a less-than-ideal concentration) after PCI is more likely to explain our clinical findings than the postulated off-target effect of bivalirudin. The absence of any signal suggesting higher ischemic hazards during or at the end of intervention (i.e., intraprocedural thrombotic events, final Thrombolysis in Myocardial Infarction [TIMI] flow grade <3, or periprocedural myocardial infarction) among patients receiving the full-dose bivalirudin regimen argues

against the possibility that the bivalirudin-induced sequestration of myeloperoxidase carries clinical implications.

We agree with Shah that the MATRIX results do not disprove the potential effectiveness of bivalirudin in reducing the risk of postintervention thrombotic events when administered after PCI in the full-dose regimen. The BRIGHT study findings were reported only after recruitment for the MATRIX trial had been completed, whereas the EUROMAX trial,⁴ which was reported in 2013, led to a strong preference for the full-dose bivalirudin regimen for patients enrolled in the post-PCI-infusion group of the MATRIX trial after that date. Ischemic risks, including stent thrombosis, were low among patients receiving the full-dose, post-PCI regimen in our study. Whether this is a real finding or the result of selection bias remains to be ascertained.

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Since publication of the article, Drs. Valgimigli and Santucci report no further potential conflict of interest.

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Chemohormonal Therapy in Hormone-Sensitive Prostate Cancer

TO THE EDITOR: Sweeney et al. (Aug. 20 issue)¹ report a marked survival advantage with concomitant docetaxel and androgen-deprivation therapy (ADT), as compared with ADT alone, in patients with hormone-sensitive metastatic prostate cancer. However, it would be interesting to compare the experimental group with the subgroup of the control group that received subsequent docetaxel after the development of castration resistance to clarify the effect of timing on patient outcomes. In addition, the survival benefit was more pronounced in high-risk patients, with an extraordinary hazard ratio of 0.61. This underlines the need for more accurate models integrating data on disease volume with patient age and coexisting conditions to avoid selection biases based only on the number and sites of metastases.

The development of molecular biomarkers to predict the biologic aggressiveness of prostate cancer or the sensitivity of tumors to a specific therapy is still in the early stages. This is partially due to tumor heterogeneity, with the coexistence of androgen-sensitive and resistant clones across different metastases.² In this sce-

nario, is it conceivable to evaluate the expression of the splice variant ARv567, a biomarker of taxanes sensitivity,³ to personalize the approach to patients who have not previously received hormone therapy?

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No potential conflict of interest relevant to this letter was reported.

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